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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,349	10/16/2001	Christiane Garbay	P07278US01/BAS	8059
881	7590	06/02/2004	EXAMINER	
STITES & HARBISON PLLC 1199 NORTH FAIRFAX STREET SUITE 900 ALEXANDRIA, VA 22314			LUKTON, DAVID	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/977,349

Applicant(s)

GARBAY ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Applicants' election of Group 1 with traverse is acknowledged (claims 1-4, 12, 13, 15, 16), as is the elected specie. Applicants traversal is noted. The non-elected groups are rejoined herewith. Claims 1-21 are examined in this Office action.



The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification provides data showing that some of the claimed peptides can bind to Grb2 *in vitro*. However, there is no evidence that such binding correlates with therapeutic efficacy in a mammal. Each of the cited claims recites one or more of the following terms: "pharmaceutical composition", "therapeutically efficient", "treatment of diseases" or "treatment of cancer". Each of these terms either explicitly states or implies therapeutic efficacy in the treatment of a human diseases. However, no

evidence is presented that there exists even one disease which can be successfully treated in a patient by administering one of the claimed compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. The following references discuss the matter of various attempts by oncologists to treat cancer:

Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results.

As mentioned on page 2 (specification) and in, e.g., Yao (*J. Med. Chem.* **42** 25, 1999); Liu (*J. Med. Chem.* **47**, 1223, 2004); and Garbay (*Biochem Pharmacol* **15**, 1165-1169, 2000), proteins containing the Grb2 SH2 domain are linked to signaling events involving RAS proteins. As it happens, attempting to treat cancer using farnesyl protein transferase inhibitors leads to "unpredictable" results:

- Moasser (*Breast Cancer Research and Treatment* **73** (2) 135-44, 2002) discloses (e.g., abstract) that FT inhibitor sensitivity does not correlate with the relative expression of Ras isoforms or the inhibition of Ras processing, growth factor signaling, expression of estrogen receptor or the overexpression of growth factor receptors. Also stated (last paragraph) is that Ras is not a molecular marker to guide FT inhibition therapy. This reference does not support the proposition that attempts to treat cancer patients will necessarily result in failure. However, it does support the proposition that there may be many forms of cancer which will be resistant to the effects of FT inhibition.
- Jiang (*Molecular and Cellular Biology* **20** (1) 139-48, 2000) discloses that while AKT2- transformed NIH 3T3 cells are sensitive to FTI-277, but that *ras*-transformed NIH 3T3 cells are not. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.
- Prendergast (*Molecular and Cellular Biology* **14** (6) 4193-202, 1994) discloses that the FT inhibitor L-739,749 inhibited growth of *ras*-transformed fibroblasts. However, L-739,749 had no effect on the growth, morphology, or actin organization of *v-raf*-transformed cells. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.
- Njoroge (*J. Med. Chem.* **40** (26) 4290-301, 1997) discloses that the Ras farnesyl-protein transferase inhibitor SCH 44342 did not show appreciable *in vivo* antitumor activity. This supports the proposition that *in vitro* activity is not necessarily predictive of therapeutic efficacy.
- Lerner (*Oncogene* **15** (11) 1283-8, 1997) discloses that the Ftase inhibitor FTI-277 is highly effective at blocking oncogenic H-Ras but not K-Ras4B processing and signaling. The results obtained demonstrate that while FTI-277 inhibits N-Ras and H-Ras processing in the human tumor cell lines evaluated, inhibition of K-Ras processing requires both an FTase inhibitor and a GGTase I inhibitor.
- Whyte (*J Biol Chem* **272**, 14459, 1997) discloses that geranylgeranyl transferase-1 is structurally related to farnesyl transferase, and that geranylgeranyl transferase-1 may alternatively prenyl K-Ras, thereby bypassing the effect of FPTase inhibition.
- Sharma (*Annals of Oncology* **13** (7) 1067-71, 2002) discloses results of a phase II trial of SCH 66336, an FPTase inhibitor, in patients with metastatic colorectal cancer. No objective responses were observed. It is concluded that future

development of this compound cannot be recommended as monotherapy in this disease.

Thus, attempts to treat cancer lead, in general, to "unpredictable" results, as do attempts to treat cancer using Ftsase inhibitors. Accordingly, it stands to reason that in attempting to treat cancer in humans using compounds which inhibit binding of a phosphopeptide to Grb2, "unpredictable" results will be obtained.

Accordingly, "undue experimentation" would be required to practice the invention of claims 12-20. It is suggested that all recitations of the term "pharmaceutical" be deleted, along with all recitations of the terms "therapeutically efficient", "treatment of diseases" and "treatment of cancer". Either or both of the following claims can be added, if deemed appropriate:

A composition comprising a pharmaceutically acceptable carrier and compound according to claim 1 in an amount effective to inhibit proliferation of tumor cells

A method of inhibiting proliferation of tumor cells comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.

In addition, if there is descriptive support for it, either of the following can be added (no determination has been made as to what might, or might not constitute new matter):

A method of inhibiting Ras-dependent signaling comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.

A method of inhibiting binding between an activated phosphotyrosine-containing receptor and Grb2 comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.



Claims 1-21 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In the claims, the term “naphthylmethyl” is misspelled. See, for example, the seventh line of text following formula I in claim 1.
- Claim 1 recites that variable R_2 can be a phenylmethyl group that is substituted with “phosphate”, “sulfonate” or “carboxylate”. The terms “phosphate”, “sulfonate” and “carboxylate”, however, could be interpreted in either of two ways: (a) a salt of phosphoric acid monoester or a salt of a sulfuric acid monoester or a salt of an aryl carboxylic acid, or (b) a phosphoric acid diester, or sulfuric acid diester or an ester of a carboxylic acid. Which is intended?
- Claim 1 recites the following (on page 2 of the claims section, third line from last):

“ R_4 ... is an *alpha, beta*-naphthyl”

What is meant by an *alpha, beta*-naphthyl...? Does this mean that both of the naphthyl isomers must be present, or does it mean that either can be present?

- In several of the claims, peptide sequences are provided. Each of these sequences should be accompanied by the appropriate **SEQ ID NO:**.
- In claim 1, it is recited that R_2 can be pyridinylmethyl or cyclohexylmethyl or naphthylmethyl which is substituted in the meta- or para position by any of the recited groups. The meaning of the terms “meta” and “para” may be somewhat clear in the case of a phenyl group, but the same cannot be said for a pyridine or cyclohexyl or naphthyl group. In the case of the pyridinylmethyl group, the “meta” position could be determined either relative to the nitrogen atom (of the pyridine ring) or the methyl group (that is bonded to the pyridine ring). In the case of the cyclohexyl group, the terms “meta” and “para” are not defined. Similarly, “meta” and “para” are not defined for naphthyl.

- In claim 2 (line 1), the term “compound” lacks antecedent basis.
- In considering the first and last lines of claim 1, it would appear that claim 1 is drawn to a pseudopeptide and pharmaceutically acceptable salts. One interpretation is that applicants are claiming a mixture of three different compounds. The first compound is a pseudopeptide, the second compound is a salt of the pseudopeptide, and the third compound is a salt of the pseudopeptide which is different from the first salt. If this is not intended, the following could be used in the last line of claim 1:
... or a pharmaceutically acceptable salt thereof.
- Claim 5 is drawn to a compound “corresponding” to that of formula II. What is meant by “corresponding”...?
- Claim 5 recites that the phenylmethyl group which is substituted by P1’ is a “precursor” of the recited groups. What is meant by a “precursor”....? Does this include synthetic intermediates?
- In claim 9, last line the following term is used: “tert.butylcarbonyl”. Accordingly, in claim 9, there are two periods; there should be just one. It is suggested that the term *tert-butylcarbonyl* be used instead. See also claim 10.
- Claim 12 is drawn to a composition. A composition must have at least two components, otherwise it is a compound. Claim 12 thus mandates the presence of a second component, yet provides no indication as to what that second component might be. If a “carrier” is intended, then perhaps this should be recited in the claim language.
- Claim 13 recites various compounds, including the following:

mAZ-pTyr-(Me)pTyr-Asn-Aha-antennapedia

mAZ-pTyr-(Me)Tyr(PO₃H₂)-Asn-Aha-antennapedia

Here, the term “antennapedia” is undefined. The term at issue refers to a gene in *Drosophila* that encodes a transcription factor. Thus, the question is does

“antennapedia” refer to a specific peptide, or to an undefined genus of peptides and proteins?

- In claim 16, the last compound listed is the following:

mAZ-pTyr-(Me)Tyr(PO₃H₂)-Asn-Aha-antennapedia

Here, “Tyr(PO₃H₂)” should instead be *Tyr(PO₃H₂)*.
See also claim 4.

- Claim 20 recites the phrase “diseases connected with proliferative processes”. It is acknowledged that the skilled artisan could determine some of what is likely encompassed. The issue here concerns the limits of what may be encompassed. For example, when an animal is stricken with a bacterial or viral infection, the bacteria or viruses “proliferate”. Would a bacterial infection be considered a “disease connected with a proliferative process”...?
- Claim 21 recites the term “automatable”, thus rendering the claim indefinite as to whether the process is ever automated or not.
- Claim 21 recites that the process must constitute a “high throughput test”. What are the criteria for “high throughput”...? How does a practitioner know when (or if) he has reached the threshold for “high throughput”...? If the practitioner is able to analyze only three compounds per day, would this be sufficient?
- Claim 21 is indefinite as to the process steps. It is recited that the compound is “made to compete” with the peptide biotin Aha-PSpYVNVQN for Grb2. By what means is the peptide persuaded to compete, and what methods does one employ if the compound is “unwilling” to compete? That is, within the claimed genus, some compounds are no doubt entirely “unwilling” to compete, i.e., inactive. Thus, how does the practitioner decide where the dividing line is between “active” and “inactive”...? More broadly, how does one determine “the affinity” of the compound for Grb2...? Is there intended to be a gradation of affinity, or are all compounds automatically deemed to have “affinity” for Grb2, regardless of the results obtained?

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600